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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).
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Express Mail Label No.

INVENTOR(S)					
Given Name (first and middle [if any])		Family Name or Surname		Residence (City and either State or Foreign Country)	
J. Kenneth		Hooper		Phoenix, Arizona	
Additional inventors are being named on the <u>1</u> separately numbered sheets attached hereto					
TITLE OF THE INVENTION (500 characters max)					
Peptide Sugar Mimetic of N-Acetylglactosamine for Use as a Potential Cancer and Pathogen Therapy					
Direct all correspondence to: CORRESPONDENCE ADDRESS					
<input checked="" type="checkbox"/> Customer Number: <div>39978</div>					
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<input type="checkbox"/> Firm or Individual Name					
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ENCLOSED APPLICATION PARTS (check all that apply)					
<input checked="" type="checkbox"/> Specification Number of Pages <u>3</u>					
<input type="checkbox"/> Drawing(s) Number of Sheets _____					
<input type="checkbox"/> Application Data Sheet. See 37 CFR 1.76					
<input type="checkbox"/> CD(s), Number _____					
<input type="checkbox"/> Other (specify) _____					
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT					
<input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27.					
<input type="checkbox"/> A check or money order is enclosed to cover the filing fees.					
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FILING FEE Amount (\$) <div>\$80.00</div>					
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.					
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Respectfully submitted,

SIGNATURE
TYPED or PRINTED NAME Joseph W. Mott
TELEPHONE 602 262-5866

[Page 1 of 2]

Date 02/04/2004
REGISTRATION NO. 35,621
(if appropriate)
Docket Number: _____

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INVENTOR(S)/APPLICANT(S)

Given Name (first and middle [if any])	Family or Surname	Residence (City and either State or Foreign Country)
Laura L.	Eggink	Scottsdale, Arizona
Valerie	Jacobs	Phoenix, Arizona

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Number 1 of 1

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PEPTIDE SUGAR MIMETIC OF *N*-ACETYLGALACTOSAMINE FOR USE AS A POTENTIAL CANCER AND PATHOGEN THERAPY

Laura L. Eggink, Valerie L. Jacobs and J. Kenneth Hooper

Rationale

Carbohydrate antigens are immune targets associated with a variety of pathogens and cancers. Lectin-carbohydrate interactions are required for macrophage-mediated toxicity toward these invaders. A human serum glycoprotein, human Vitamin D-Binding protein, with known macrophage activating activity, can be administered as a therapy against cancers and pathogens (1,2). Unfortunately, viruses and cancers produce glycosidases which cleave sugar moieties from natural and man-made therapeutic antigens and thereby inactivate the protein. Molecular mimics of carbohydrates presents a novel and stable alternative source of compounds to target pathways involving protein-carbohydrate interactions. Expected outcome: The peptide mimetic therapy will not require a *N*-acetylgalactosamine (GalNAc), which is difficult to produce and is easily inactivated. The peptide mimetic will have all the activity of human Vitamin D-Binding protein but will possess greater stability and ease of synthesis. Additionally, the sequence of the active site is novel and without homology to current patents held on Vitamin D-Binding protein.

Summary of the Invention

We have discovered a 12-mer peptide sequence that mimics a required GalNAc of a macrophage activating factor, as determined by binding to a GalNAc specific lectin. To increase stability and reactivity, this peptide may be fused to a protein carrier, such as the C-terminus of human Vitamin D-Binding protein. It has been previously shown that peptide sugar mimetics can induce functional carbohydrate cross-reactive immune

responses in pathogen and tumor models (3). Therefore, this fusion peptide is expected to be active in the therapeutic remission of cancer and biological inactivation of pathogen infection. Peptide mimetics also have an advantage in that they can be synthesized in prokaryotic organisms. Because of the novelty of this invention, a suite of patents may be filed in support of the peptide sugar mimetic, which may include intellectual property covering activity and delivery of the peptide. This cluster would provide an attractive portfolio to interested licensees.

Construction of GalNAc Peptide Mimetic

Combinatorial peptide libraries displayed on phage M13 provided approximately 3×10^9 variants of a 12-amino acid sequence. Each of these sequences were present in about 55 copies. The total library was screened with a GalNAc-specific lectin to search for a peptide mimetic of the sugar. Phage particles that bound to the lectin were eluted with free GalNAc and the process was repeated several times. After DNA of phage that were selected by this procedure were sequenced, a unique consensus amino acid sequence of VQATQSNOHTPR emerged. Insertion of variations of this sequence should allow construction of a series of fusion peptides with which binding affinities and consequently activity can be manipulated to achieve optimal clinical results.

[Commercialization of sequences discovered using Ph.D.TM, a trademark of New England Biolabs, Inc., may require a license from Dyax Corp.]

Testing the Hypothesis

Branched and linear peptides containing the mimetic sequence were synthesized by solid-phase methods using standard Fmoc side chain protection. The branched peptide was constructed on a poly-lysine core consisting of 4 branches containing a linker

sequence of GGGS and a dansylated C-terminal cysteine. The linear peptide also contained the linker sequence GGGS, a dansyl group and was C-terminally linked to a polystyrene bead. Human monocyte cell line THP-1 and mouse monocyte cell line WEHI-3 have been purchased for macrophage activation assays. Assays for activation will include oxidative burst assays, cytochrome C reduction assays, and fluorescence microscopy. In addition, N-terminally linked cross-linking reactive groups will be appended to the linear peptide for immunoprecipitation assays. The peptides will be crosslinked to the macrophage lectin receptor during activation and the immunoprecipitated complex will be sequenced by mass spectrometry. Identification of the receptor may lead to additional patent coverage.

For *in vivo* production of a GalNAc peptide mimetic fusion protein, panning of a C7C Phage Display Peptide Library kit based on combinatorial library of random 7-mers flanked by a pair of cysteine residues is currently underway. Disulfide constrained peptides will be useful in maintaining the structural integrity of the mimetic. This sequence will be incorporated into the C-terminal loop domain of human Vitamin D-Binding protein and overexpressed in the appropriate host.

- (1) Yamamoto N, Naraparaju VR, Srinivasula SM (1995) Structural modification of serum Vitamin D₃-Binding protein and immunosuppression in AIDS patients. *AIDS Res Human Retroviruses* 11:1373-1378
- (2) Yamamoto N, Naraparaju VR (1997) Immunotherapy in BALB/c mice bearing Ehrlich ascites tumor with Vitamin D-Binding protein-derived macrophage activating factor. *Cancer Res* 57:2187-2192
- (3) Monvazi-Karbassi B, Cunto-Amesty G, Luo P, Kieber-Emmons T (2002) Peptide mimotopes as surrogate antigens of carbohydrates in vaccine discovery. *Trends Biotechnol* 20:207-14